CRF Completion

Study AC-060A202: CONTROL

Miyuki Tomioka

ACTELION

AC-060A202 CRF Overview

Collection of data on 3 different documents:

1. **Core CRF**

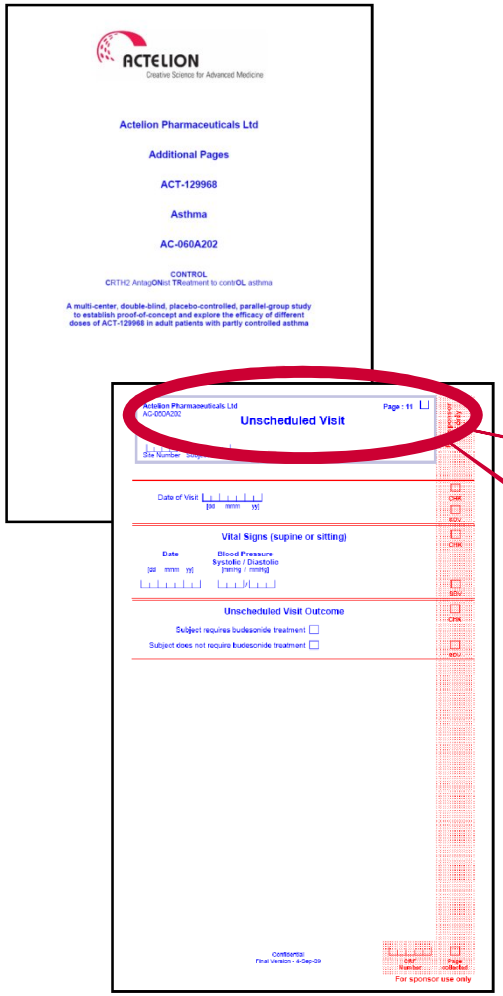
2. **Additional Pages Binder**

- **Only for randomized patients**
- **To be completed:**
  - **by the PI or co-investigator**
  - **using a digital pen**

3. **Questionnaire Booklet**
   - ACQ
   - AQLQ(S)
   - Nasal Symptoms VAS

- **For each screened patient**
- **To be completed:**
  - **mainly by the patient, but partly by site staff**
  - **using a regular ink pen**

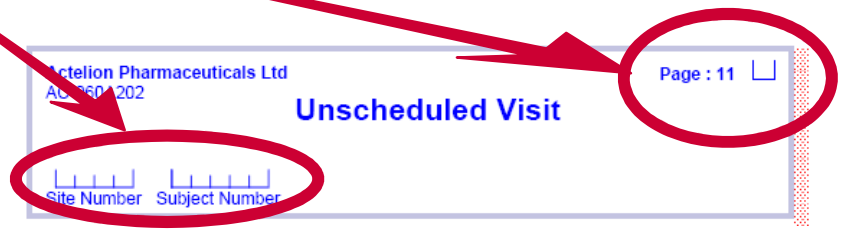
Additional Pages Pads



Contains additional pages for

- Unscheduled Visits
- Adverse Events
- Concomitant Medications

Pages have no BARCODE.



Core CRF Completion Instructions (1/2)

- Complete a CRF **only** for patients who have been randomized
  - **No CRF** for screening failure patients

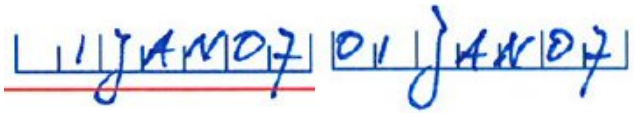
- Only authorized person should complete the CRF
  - Only PI or co-investigator can sign on the study completion page

- Complete the CRF using a digital pen (DP) **only**
  - One DP will be provided to the site at initiation visit
  - The DP must be used for all entries and corrections

Core CRF Completion Instructions (2/2)

- Write clearly and use **only** the Digital Pen
- Use letters for the month in English:

- Do not leave fields empty. Use a leading “0”:



- Use the 24-hour clock (e.g. Noon = 12:00; 4.15PM = 16:15; Midnight = 24:00)
- If you do not have data there are 2 possibilities:
  - **NK/NKK** = Not Known
  - **ND** = Not Done

- Errors should be crossed out using a single line (e.g., ~~mistake~~)

Page “0” (Cover page)

On the randomization day, please enter the following information with DP:

Site No.

(4 digits allocated by Actelion)

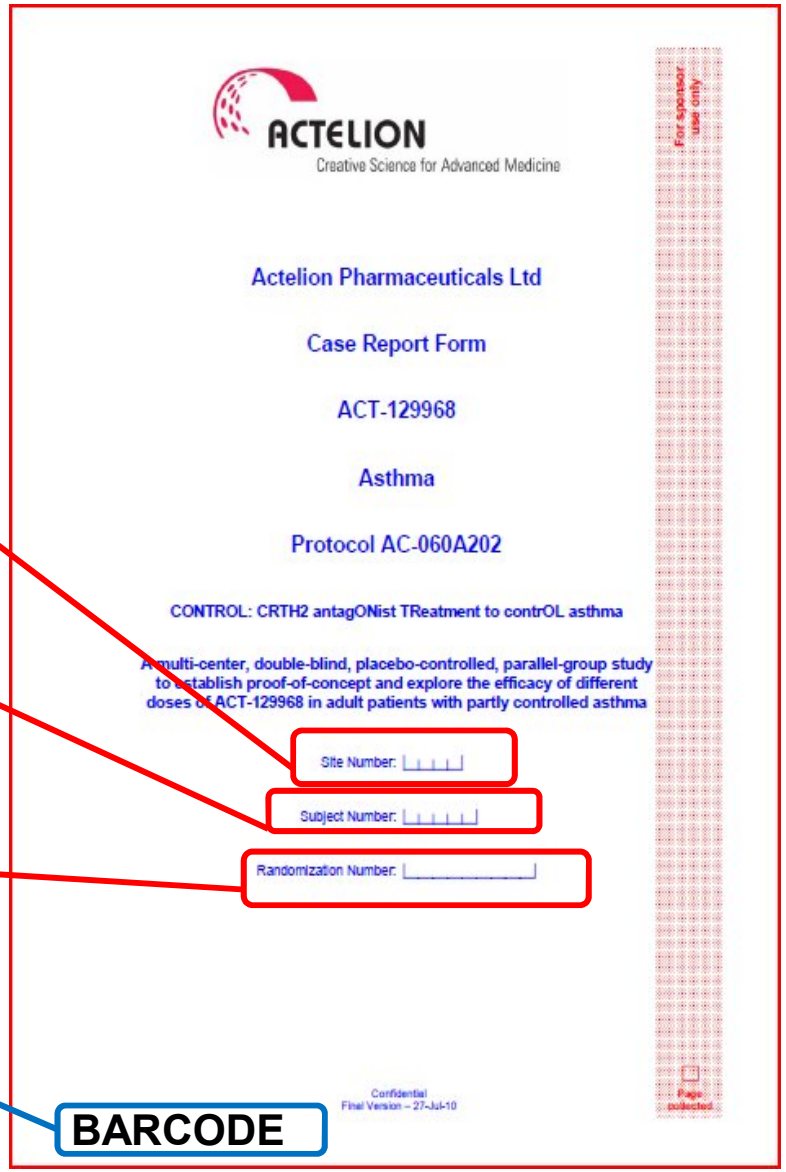
Subject No.

(5 digits allocated by ICON at the time of screening via IVRS/IWRS)

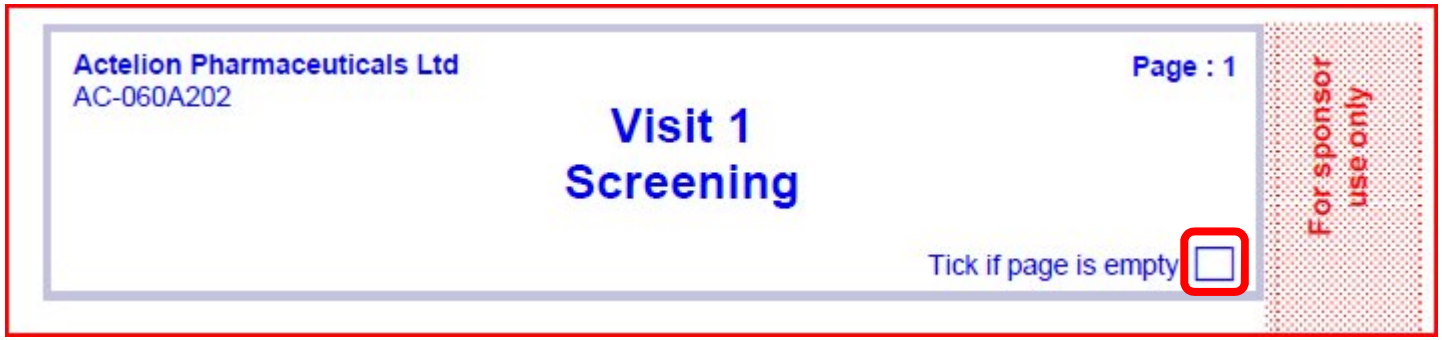
Randomization No.

(4 digits allocated by ICON at the time of randomization via IVRS)

This page 0 (incl. barcode) will link the CRF and the subject number.



Core CRF
All pages

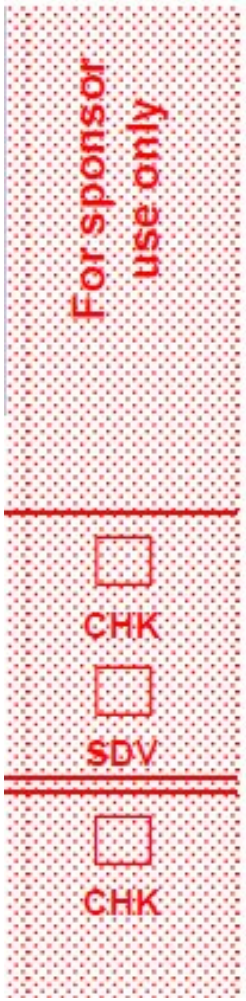


Tick if page is empty

(filled by the investigator)

Core CRF
All pages

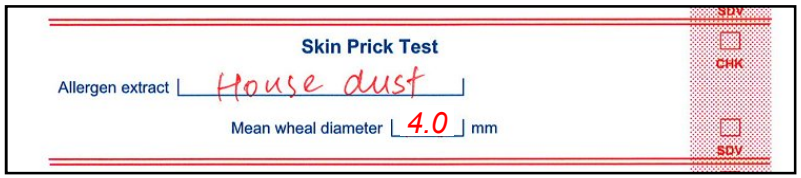
“Redstrip” on the right hand site of the CRF is exclusively reserved for the RM/Actelion



Skin prick test (SPT) – Visit 1

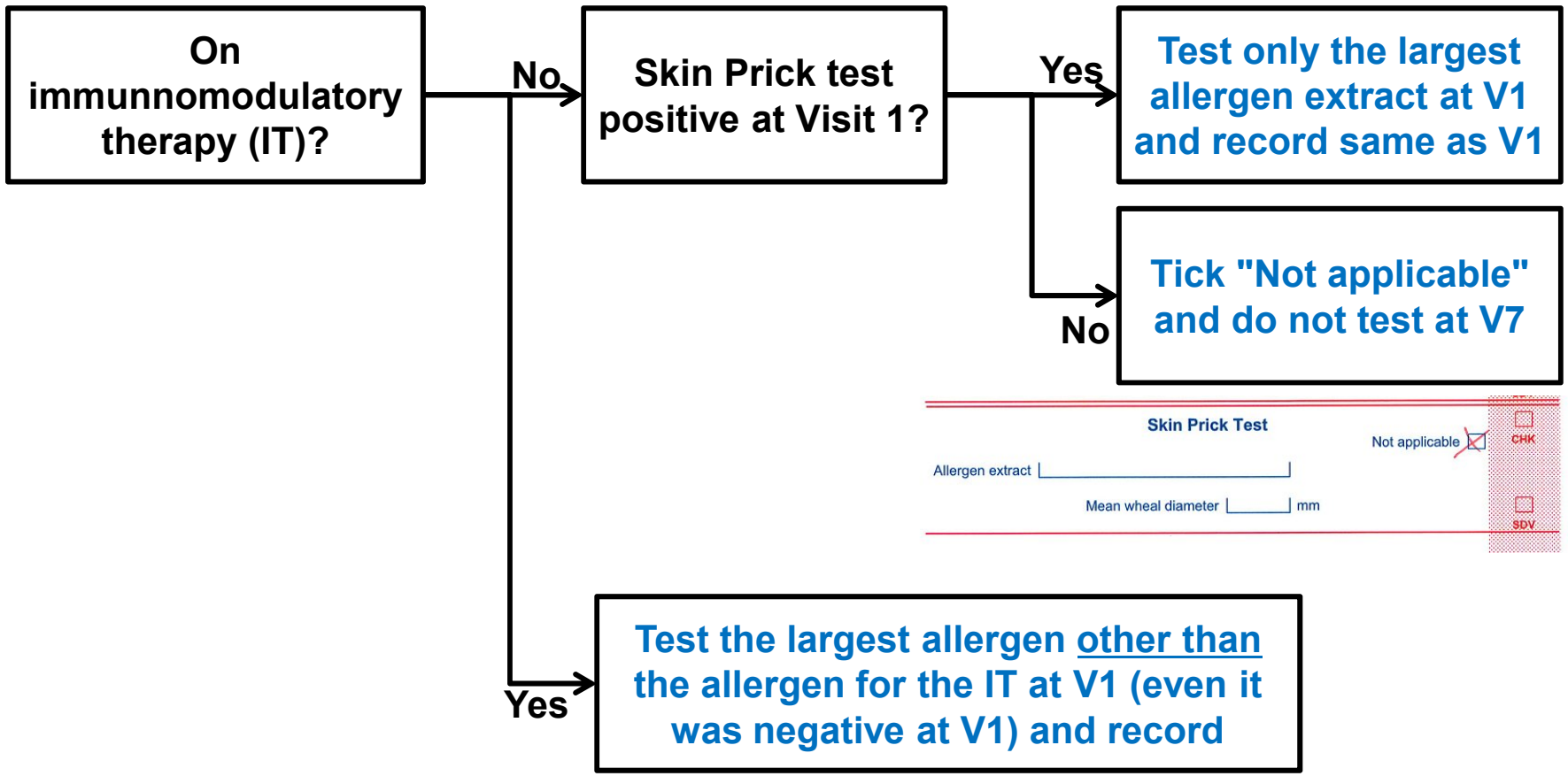
Visit 1

- Record allergen extract that had **the largest mean wheal diameter** from all tested allergen extracts.
  - ✓ If the patient is **on immunomodulatory therapy** for the allergen producing the largest wheal, **record the second largest** mean diameter.



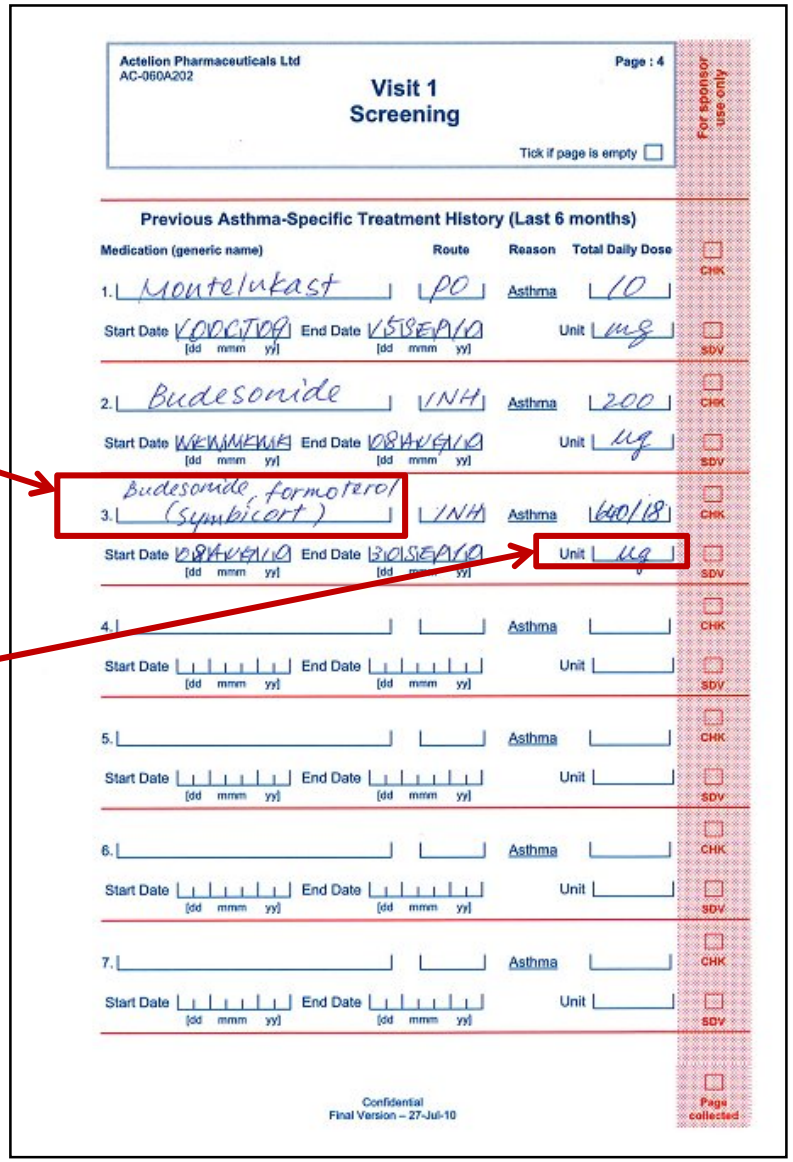
Skin prick test (SPT) –Visit 7(EOT)

<u>Visit 7:</u> If positive at Visit 1 Test only one allergen extract which was the largest mean wheal diameter at Visit 1. If on immunomodulatory Therapy:



Previous Asthma-Specific Treatment History (last 6 months) – Visit 1

- Record all asthma-specific treatment within 6 months prior to the screening
- Use only <u>generic name</u> of the medication, <u>except for combination drugs</u>.
  - For combination drugs, enter the generic name and put the brand name in parenthesis.
- <u>Record unit as weight</u> (e.g. mg, µg), not tablets or capsules.
- For “as-needed basis” reliever medication, enter “PRN” instead of the dose and leave the unit blank.



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Page : 4

Visit 1
Screening

Tick if page is empty ☐

For sponsor use only

Previous Asthma-Specific Treatment History (Last 6 months)

	Medication (generic name)	Route	Reason	Total Daily Dose
1.	Montelukast	PO	Asthma	10
	Start Date 10OCT09 [dd mmm yy] End Date 15SEP10 [dd mmm yy]			Unit mg
2.	Budesonide	INH	Asthma	200
	Start Date 14MAY08 [dd mmm yy] End Date 08AUG10 [dd mmm yy]			Unit ug
3.	Budesonide, formoterol (Symbicort)	INH	Asthma	160/18
	Start Date 08AUG10 [dd mmm yy] End Date 30SEP10 [dd mmm yy]			Unit ug
4.			Asthma	
	Start Date [dd mmm yy] End Date [dd mmm yy]			Unit
5.			Asthma	
	Start Date [dd mmm yy] End Date [dd mmm yy]			Unit
6.			Asthma	
	Start Date [dd mmm yy] End Date [dd mmm yy]			Unit
7.			Asthma	
	Start Date [dd mmm yy] End Date [dd mmm yy]			Unit

CHK SDV

Page collected

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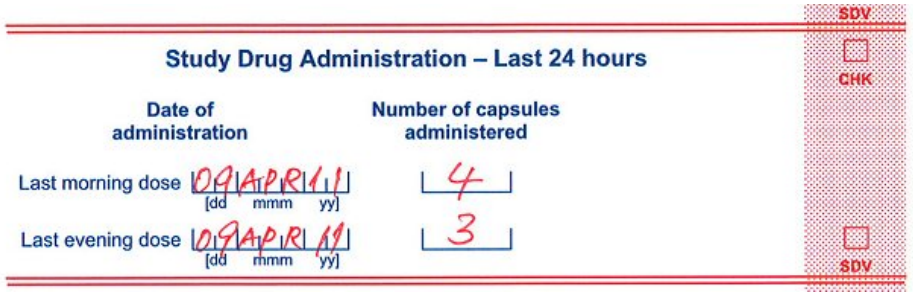
Final Version – 27-Jul-10

Study drug administration and PK sampling - Visit 3-7 and Unscheduled Visits

Study Drug Admin – Last 24hrs:

•Enter the date of the last morning dose and the date of the last evening.

•Enter the number of capsules taken by the subject at each dose



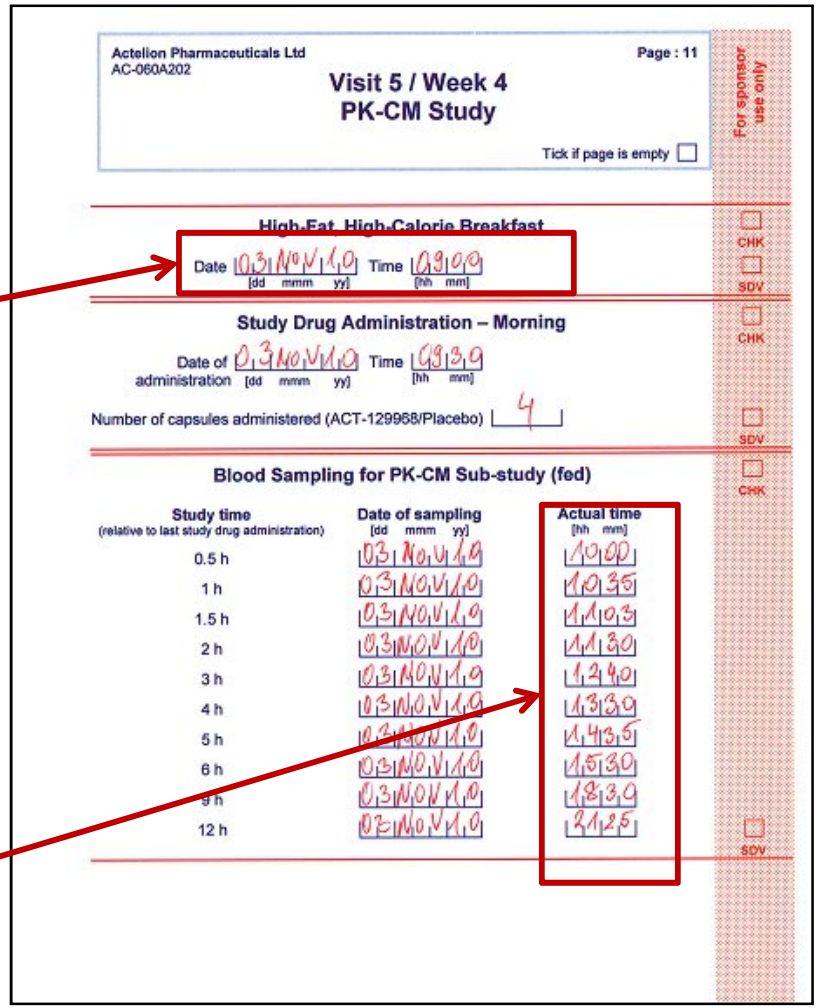
PK Sampling:

•This is the trough pre-morning dose PK sampling that should be collected from ALL patients

•Enter the date and time of sampling

PK-CM Sub-study – Visit 4 & 5

- Only complete this page if patient is participating in the PK-CM sub-study.
- Enter the starting time
  - Complete meal should be consumed within the 30 min before drug administration
- Enter the date at least for 0.5h sampling. If all samples are taken on the same day, leave the subsequent date fields empty.
- Enter the "actual" time and not the scheduled time.



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Visit 5 / Week 4
PK-CM Study

Tick if page is empty ☐

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High-Fat, High-Calorie Breakfast

Date 03 NOV 10 [dd mmm yy] Time 0900 [hh mm]

CHK SDV

Study Drug Administration – Morning

Date of administration 03 NOV 10 [dd mmm yy] Time 0930 [hh mm]

CHK

Number of capsules administered (ACT-129968/Placebo) 4

SDV

Blood Sampling for PK-CM Sub-study (fed)

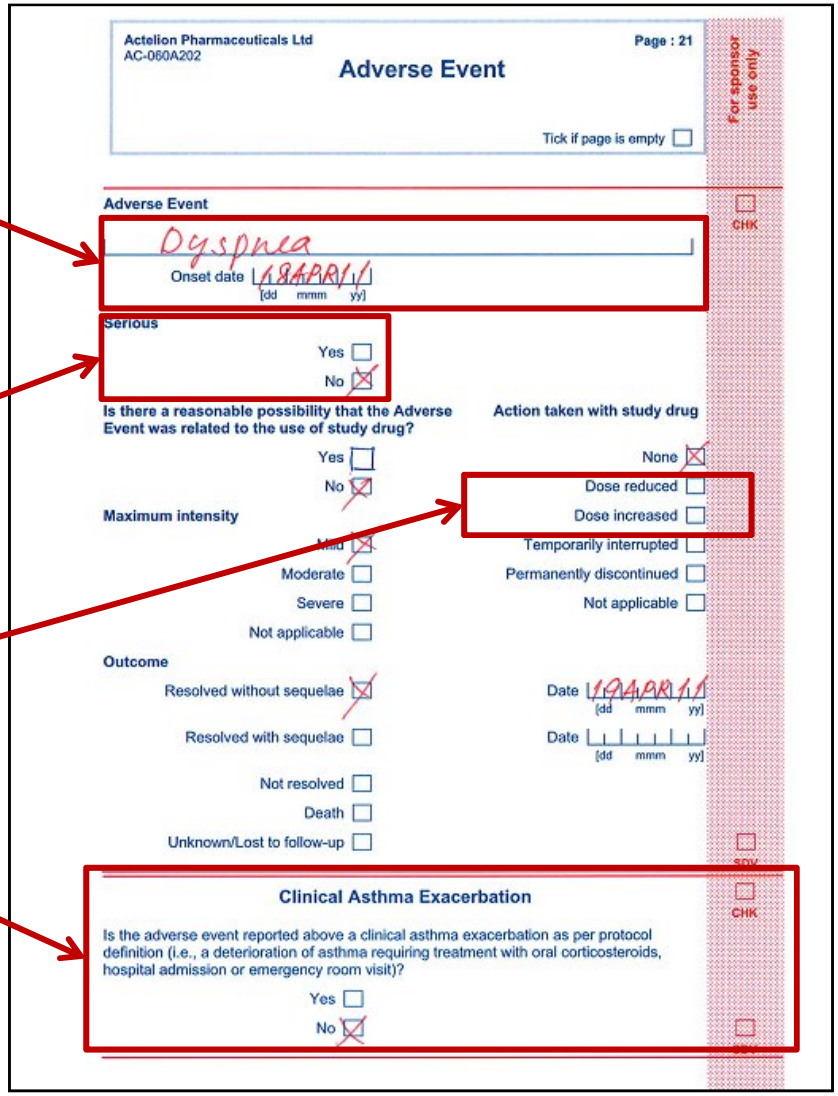
CHK

Study time (relative to last study drug administration)	Date of sampling [dd mmm yy]	Actual time [hh mm]
0.5 h	03 NOV 10	1000
1 h	03 NOV 10	1035
1.5 h	03 NOV 10	1103
2 h	03 NOV 10	1130
3 h	03 NOV 10	1240
4 h	03 NOV 10	1330
5 h	03 NOV 10	1435
6 h	03 NOV 10	1530
9 h	03 NOV 10	1830
12 h	03 NOV 10	2125

SDV

Adverse Event CRF

- Record the diagnosis and onset date.
  - If there is no diagnosis, enter the most relevant sign/symptom.
- If yes (= serious), complete an SAE form and report to Actelion Drug Safety (within 24 hours of the investigator's first knowledge)
- Not applicable in this study
- This has to be assessed in each AE.
  - Clinical asthma exacerbation always needs to be recorded as an AE.



AE/SAE Follow-up

- AEs still ongoing 4 days after treatment must be followed up until:
  - Thirty days after stopping study drug
  - Resolution
  - Stabilization

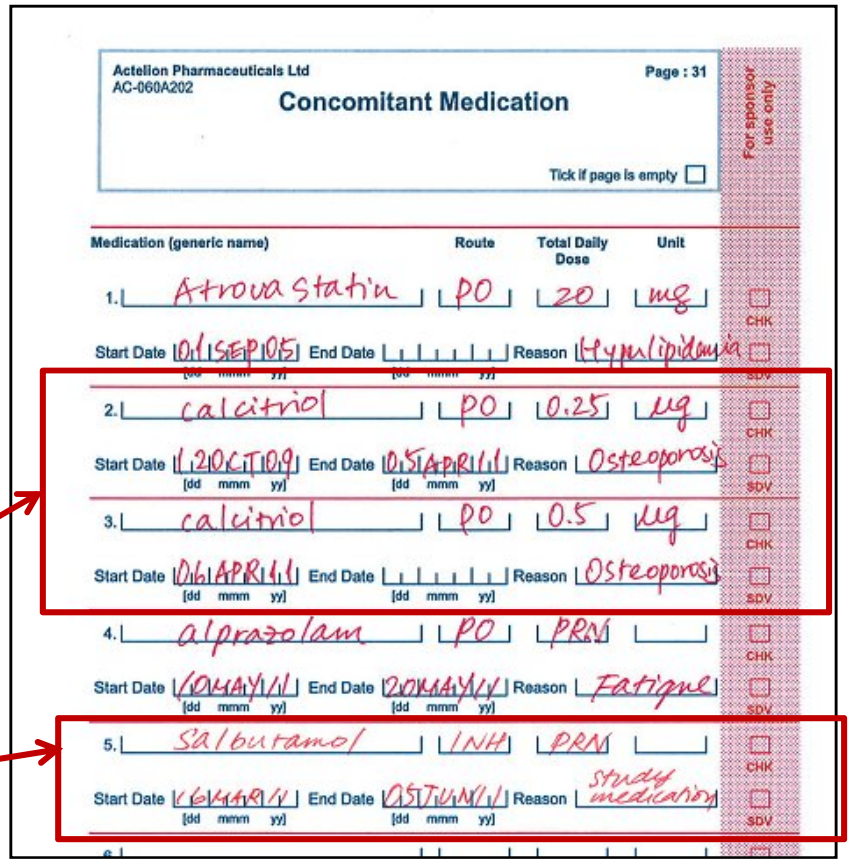
  OR
  - The event is otherwise explained

- SAEs still ongoing at the EOS visit must be followed up until:
  - Resolution
  - Stabilization

  OR
  - The event is otherwise explained

Concomitant medication

- List all medications between Visit 1 (Screening) and Visit 8 (EOS), except study drug.
- Use only generic name, except for combi.
- Record unit as weight (e.g. mg, µg).
- A new entry must be made every time the daily dose changes.
- "Salbutamol/albuterol" should be included if it is taken by the patient.



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Concomitant Medication

Tick if page is empty ☐

For sponsor use only

	Medication (generic name)	Route	Total Daily Dose	Unit	
1.	Atrovastatin	PO	20	mg	CHK
	Start Date 01SEP05	End Date	Reason Hyperlipidemia		SDV
2.	calcitriol	PO	0.25	µg	CHK
	Start Date 20OCT09	End Date 01APRIL	Reason Osteoporosis		SDV
3.	calcitriol	PO	0.5	µg	CHK
	Start Date 01APRIL	End Date	Reason Osteoporosis		SDV
4.	alprazolam	PO	PRN		CHK
	Start Date 10MAY	End Date 20MAY	Reason Fatigue		SDV
5.	Salbutamol	INH	PRN		CHK
	Start Date 16MAR	End Date 01JUN	Reason study medication		SDV
6.					

Study Completion or Permanent Discontinuation

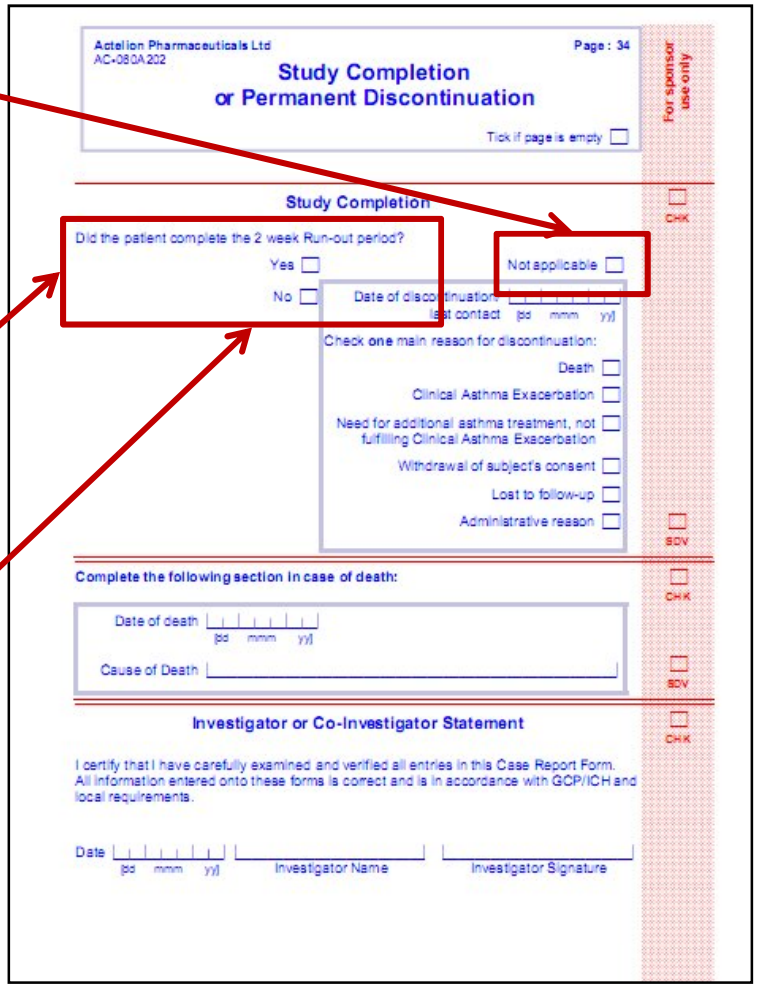
- This page must be completed for all patients.

➢ If patient discontinued during treatment then tick “NA”

➢ Discontinuation details recorded on study drug log

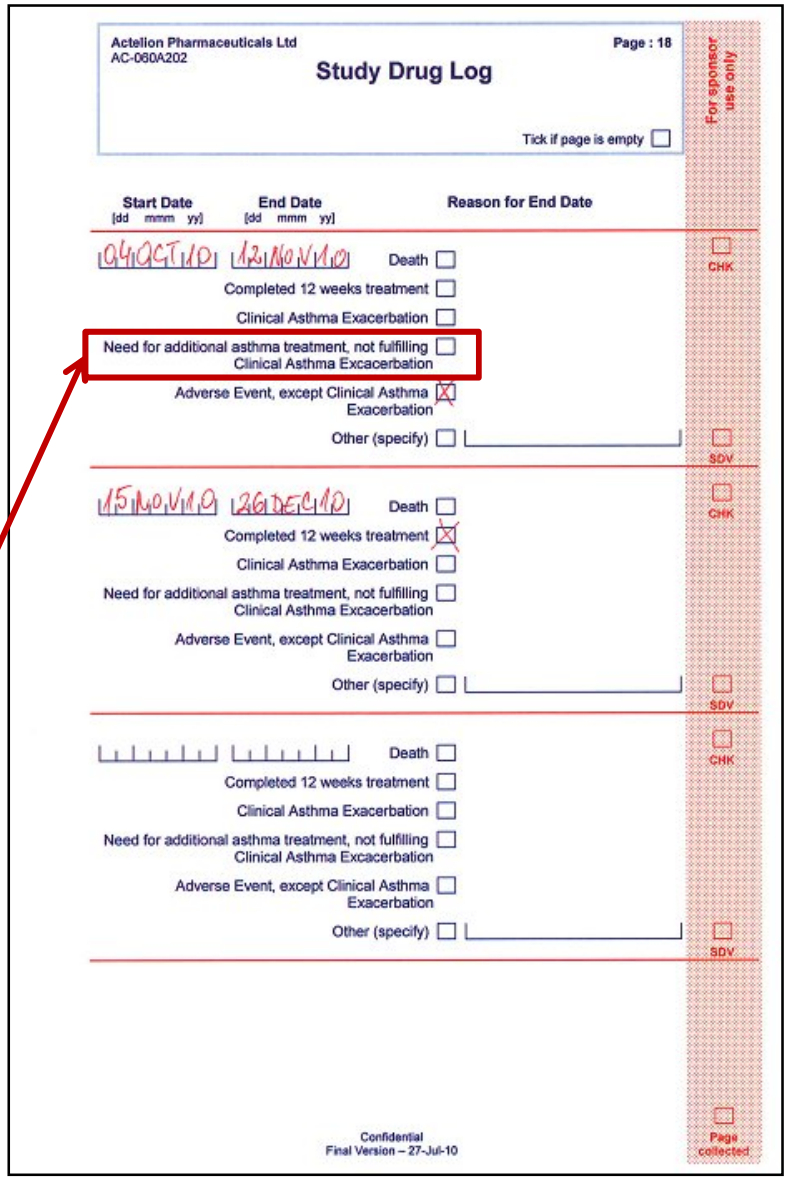
➢ If patient completed 12 weeks treatment and 2 weeks run-out answer “Yes”

➢ If patient completed 12 weeks treatmemnt but did not complete 2 weeks run-out answer “No” and complete date and reason for discontinuation



Study Drug Log

- Complete one line each time if drug admin. (incl. dose) is changed.
  - NOTE: **Any dose change should be avoided**.
- Interruptions should be for <u>less than 4 days</u>; longer interruptions should be permanent discontinuation.
- "Need for additional asthma treatment, not fulfilling Clinical Asthma Exacerbation"
  - The patient has asthma symptoms that in the judgment of the investigator require additional asthma treatment, but not clinical asthma exacerbation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Study Drug Log

Tick if page is empty

For sponsor use only

Start Date [dd mmm yy] | End Date [dd mmm yy] | Reason for End Date

04OCT10 | 12NOV10
- Death
- Completed 12 weeks treatment
- Clinical Asthma Exacerbation
- Need for additional asthma treatment, not fulfilling Clinical Asthma Exacerbation
- Adverse Event, except Clinical Asthma Exacerbation [X]
- Other (specify)

CHK | SDV

15NOV10 | 26DEC10
- Death
- Completed 12 weeks treatment [X]
- Clinical Asthma Exacerbation
- Need for additional asthma treatment, not fulfilling Clinical Asthma Exacerbation
- Adverse Event, except Clinical Asthma Exacerbation
- Other (specify)

CHK | SDV

| |
- Death
- Completed 12 weeks treatment
- Clinical Asthma Exacerbation
- Need for additional asthma treatment, not fulfilling Clinical Asthma Exacerbation
- Adverse Event, except Clinical Asthma Exacerbation
- Other (specify)

CHK | SDV

Page collected

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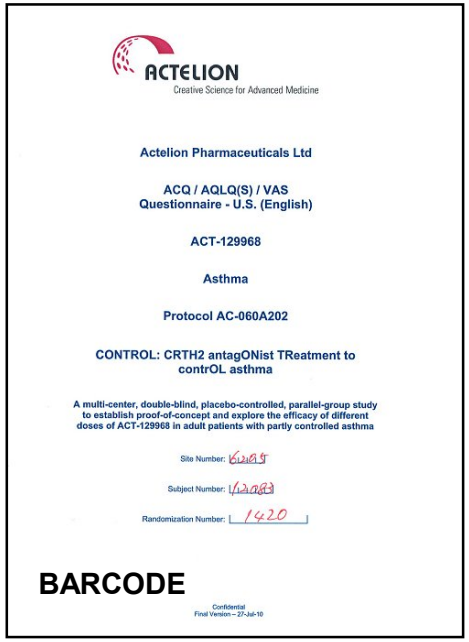
Questionnaire Booklet – Instructions

- To be completed by <u>each screened patient from Visit 1</u> (Screening visit, after the ICF signed) in their own handwriting using a <u>regular ink pen</u>.
- To be completed prior to any other assessments at each visit
- Prior to randomization at Visit 2, all subjects should complete the questionnaire for the Visit 2.
  - If a patient is randomized, the randomization number from the IVRS/IWRS should be entered in the cover page of the questionnaire booklet.
  - If a patient is <u>not</u> randomized, the used questionnaire booklet/binder should be kept as a source document at the site, but not be sent to the sponsor.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ACQ / AQLQ(S) / VAS
Questionnaire - U.S. (English)

ACT-129968

Asthma

Protocol AC-060A202

CONTROL: CRTH2 antagONist TReatment to contrOL asthma

A multi-center, double-blind, placebo-controlled, parallel-group study to establish proof-of-concept and explore the efficacy of different doses of ACT-129968 in adult patients with partly controlled asthma

Site Number: 6205

Subject Number: 62068

Randomization Number: 1420

BARCODE

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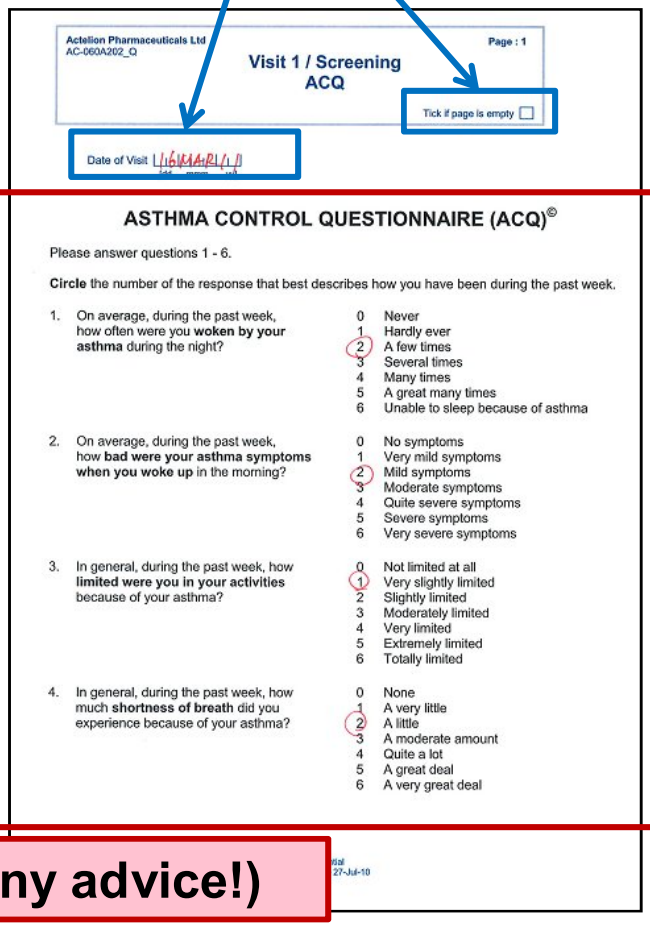
Final Version – 27-Jul-10

ACQ (Asthma Control Questionnaire): Example

- Seven questions, one-week recall
- Self-administrated by the patient at all study Visits and at all any Unscheduled Visits
  - ✓ One of the inclusion criteria

To be filled by site staff



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AC-060A202_Q

Page : 1

Visit 1 / Screening
ACQ

Tick if page is empty ☐

Date of Visit

ASTHMA CONTROL QUESTIONNAIRE (ACQ)©

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   0 Never
   1 Hardly ever
   (2) A few times
   3 Several times
   4 Many times
   5 A great many times
   6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   0 No symptoms
   1 Very mild symptoms
   (2) Mild symptoms
   3 Moderate symptoms
   4 Quite severe symptoms
   5 Severe symptoms
   6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   0 Not limited at all
   (1) Very slightly limited
   2 Slightly limited
   3 Moderately limited
   4 Very limited
   5 Extremely limited
   6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   0 None
   1 A very little
   (2) A little
   3 A moderate amount
   4 Quite a lot
   5 A great deal
   6 A very great deal

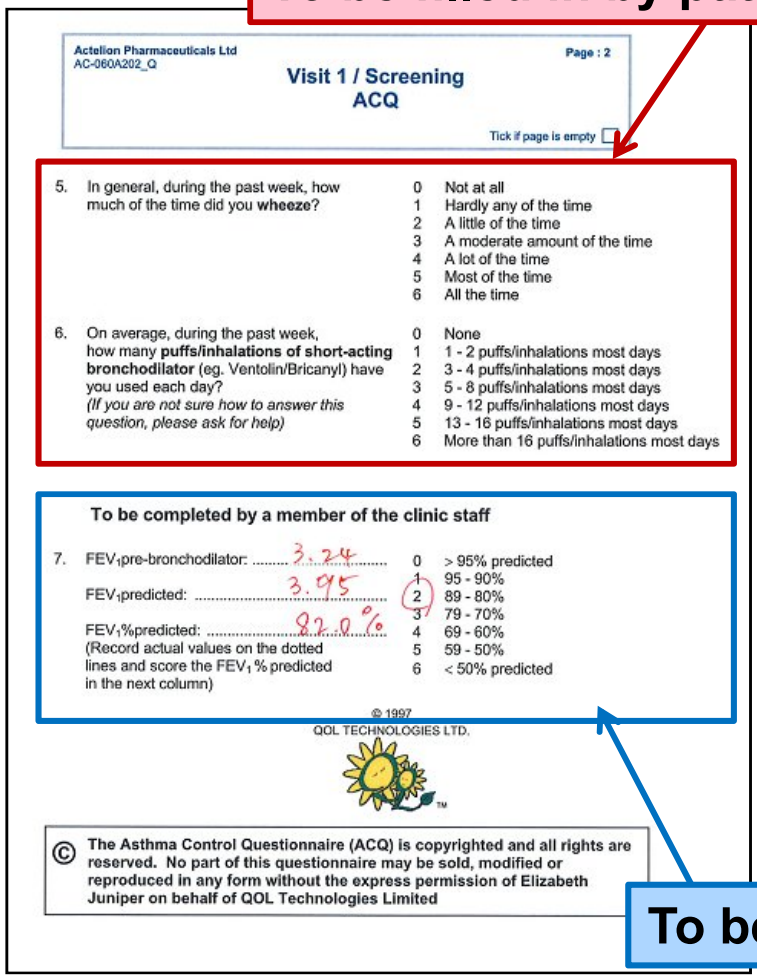
27-Jul-10

To be filled in by patient (without any advice!)

ACQ: Example (cont.)

(Russian for Russia)

To be filled in by patient (without any advice!)



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AC-060A202_Q
Page : 2

Visit 1 / Screening
ACQ

Tick if page is empty ☐

5. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
	1	1 - 2 puffs/inhalations most days
	2	3 - 4 puffs/inhalations most days
	3	5 - 8 puffs/inhalations most days
	4	9 - 12 puffs/inhalations most days
	5	13 - 16 puffs/inhalations most days
	6	More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7. FEV_1pre-bronchodilator: 3.24	0	> 95% predicted
FEV_1predicted: 3.95	1	95 - 90%
	(2)	89 - 80%
FEV_1%predicted: 82.0 %	3	79 - 70%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	4	69 - 60%
	5	59 - 50%
	6	< 50% predicted

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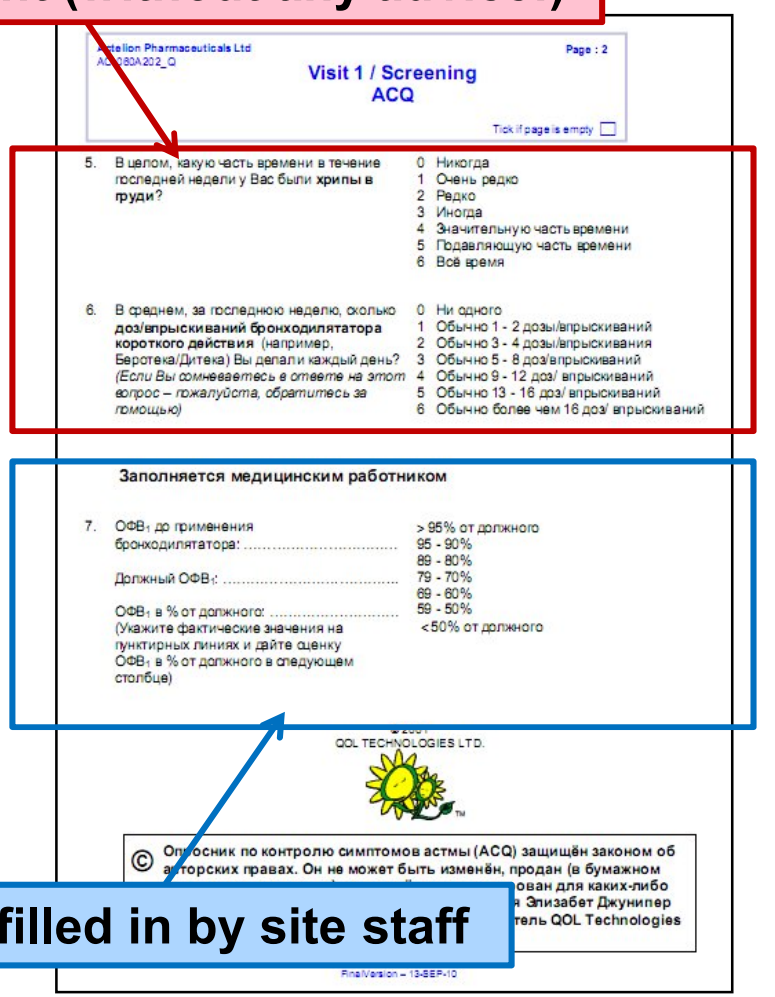

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AC-060A202_Q
Page : 2

Visit 1 / Screening
ACQ

Tick if page is empty ☐

5. В целом, какую часть времени в течение последней недели у Вас были **хрипы в груди**?	0	Никогда
	1	Очень редко
	2	Редко
	3	Иногда
	4	Значительную часть времени
	5	Подавляющую часть времени
	6	Всё время
6. В среднем, за последнюю неделю, сколько **доз/впрыскиваний бронходилятатора короткого действия** (например, Беротека/Дитека) Вы делали каждый день? *(Если Вы сомневаетесь в ответе на этот вопрос – пожалуйста, обратитесь за помощью)*	0	Ни одного
	1	Обычно 1 - 2 дозы/впрыскиваний
	2	Обычно 3 - 4 дозы/впрыскивания
	3	Обычно 5 - 8 доз/впрыскиваний
	4	Обычно 9 - 12 доз/ впрыскиваний
	5	Обычно 13 - 16 доз/ впрыскиваний
	6	Обычно более чем 16 доз/ впрыскиваний

Заполняется медицинским работником

7. $ОФВ_1$ до применения бронходилятатора:	> 95% от должного
	95 - 90%
	89 - 80%
Должный $ОФВ_1$:	79 - 70%
	69 - 60%
$ОФВ_1$ в % от должного:	59 - 50%
(Укажите фактические значения на пунктирных линиях и дайте оценку $ОФВ_1$ в % от должного в следующем столбце)	<50% от должного

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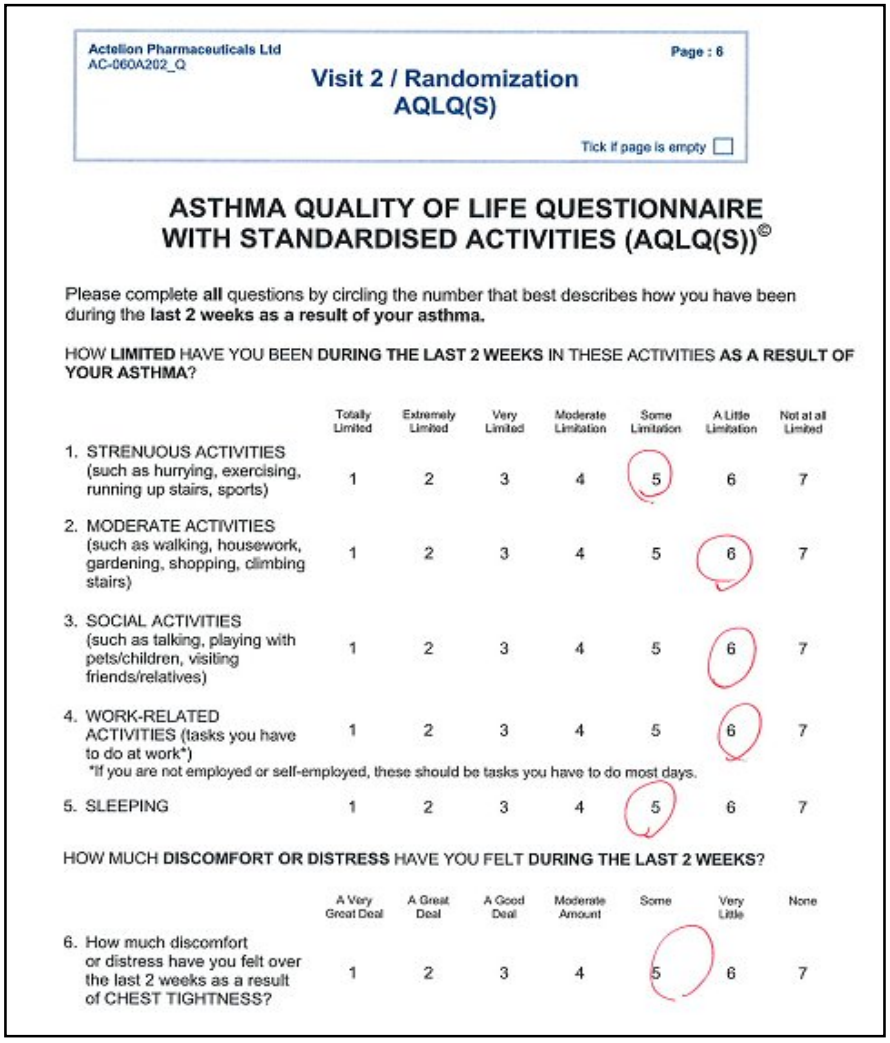
Final Version – 13-SEP-10

To be filled in by site staff

AQLQ (Asthma Quality of Life Questionnaire): Example

- Thirty-two questions in four domains (i.e., physical, emotional, social and occupational)
- Two-week recall
- Assessed by the patient at Visits 2, 4, 5, 6, 7, 8 and at all any Unscheduled Visits



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AC-060A202_Q

Page : 6

Visit 2 / Randomization
AQLQ(S)

Tick if page is empty ☐

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))©

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

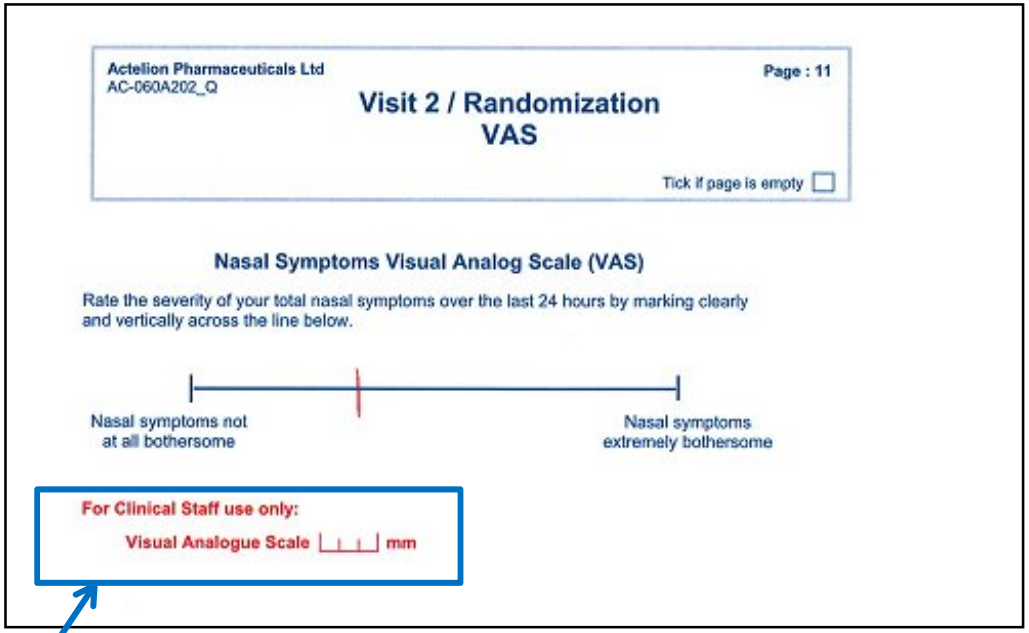
	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*) *If you are not employed or self-employed, these should be tasks you have to do most days.	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Nasal Symptoms VAS: Example

- Patient report their nasal symptoms over the last 24 hours
- Assessed by the patient at Visits 2 through 8 and at all any Unscheduled Visits



To be filled in by site staff

Data Correction and Subject Statement: Example

- If a patient makes a mistake and corrects data, fill in “Data Correction & Subject Statement” page
- However, even if incompletion is found at a later date, patients cannot be updated.
- The correction page will not be collected, and remain in the questionnaire booklet.

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AQLQ(S)

Tick if page is empty ☐

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7

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Visit 2 / Randomization
Data Correction & Subject Statement

Tick if page is empty ☐

Data Correction Log & Subject Statement

Line	Date	Page number	Questionnaire name	Question number
1	03 APR 11	08	ACQ ☐ AQLQ(S) ☒ VAS ☐	19
2			ACQ ☐ AQLQ(S) ☐ VAS ☐	
3			ACQ ☐ AQLQ(S) ☐ VAS ☐	
4			ACQ ☐ AQLQ(S) ☐ VAS ☐	
5			ACQ ☐ AQLQ(S) ☐ VAS ☐	
6			ACQ ☐ AQLQ(S) ☐ VAS ☐	
7			ACQ ☐ AQLQ(S) ☐ VAS ☐	
8			ACQ ☐ AQLQ(S) ☐ VAS ☐	
9			ACQ ☐ AQLQ(S) ☐ VAS ☐	
10			ACQ ☐ AQLQ(S) ☐ VAS ☐	
11			ACQ ☐ AQLQ(S) ☐ VAS ☐	
12			ACQ ☐ AQLQ(S) ☐ VAS ☐	
13			ACQ ☐ AQLQ(S) ☐ VAS ☐	
14			ACQ ☐ AQLQ(S) ☐ VAS ☐	
15			ACQ ☐ AQLQ(S) ☐ VAS ☐	

I certify that I have entered answers to the ACQ and AQLQ(S) and completed the Visual Analog Scale (VAS) as accurately as I could and in a timely manner.

I certify that corrections on line(s) 1 as recorded above have been done by me.

Date 03 APR 11 [dd mmm yy]

Subject's Signature